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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/337,893	06/21/1999	ARTHUR M. KRIEG	C1039/7022HC	9627

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EXAMINER	
MINNIFIELD, NITA M	
ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 03/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/337,893	KRIEG, ARTHUR M.	
	Examiner	Art Unit	
	N. M. Minnifield	1645	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42,45-53 and 57-60* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42,45-53 and 57-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892) 10 sheets

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/04/04; 10/28/04*. 12 sheets total

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.

5) ☐ Notice of Informal Patent Application (PTO-152)

6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

1. Applicant's amendments filed October 4, 2004 and November 15, 2004 are acknowledged and have been entered. Claims 1-41, 43, 44 and 54-56 have been canceled. Claim 42 has been amended. New claims 59 and 60 have been added. Claims 42, 45-53 and 57-60 are now pending in the present application. All rejections have been withdrawn in view of Applicant's amendment to the claims and/or comments. However, a new ground of rejection has been set forth (see below) and the pending office action is non-final.

2. The disclosure is objected to because of the following informalities: the ATCC address is incorrect, see p. 59 for example. Appropriate correction is required. The current address of the ATCC is as follows:

American Type Culture Collection
10801 University Boulevard
Manassas, VA 20110-2209

3. The interlineations or cancellations made in the specification or amendments to the claims could lead to confusion and mistake during the issue and printing processes. Accordingly, the entire specification is required to be rewritten before passing the case to issue. See 37 CFR 1.125 and MPEP § 608.01(q). It is not clear to the Examiner what has been amended in the specification. A clean copy of the specification is required.

4. The information disclosure statement filed October 28, 2004 has been considered.

5. The information disclosure statement filed October 4, 2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each U.S. and foreign patent; each publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been considered.

It is noted that a few of the references cited (C37, C51, C64 and C144) on the October 4, 2004 IDS were not provided. The references initialed as having been considered were available in this or other related applications. If Applicants wish all cited references to be considered a copy of those references not initialed on the October 4, 2004 IDS should be provided for Examiner consideration.

6. Claims 42, 45-53 and 57-60 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for redirecting a subject's (murine model) immune response from a Th2 to a Th1, comprising administering to a subject an immunostimulatory nucleic acid (CpG, specifically SEQ ID NO: 10), does not reasonably provide enablement for a method for redirecting a subject's (animal or human) immune response from a Th2 to a Th1 immune response, comprising administering to a subject (animal or human) an immunostimulatory nucleic acid (CpG, the scope of the myriad possible immunostimulatory nucleic acids encompassed by the formulas as set forth in claims 42, 53 and 59 for example). The specification does not enable any person

skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claims are directed to a method for redirecting a subject's immune response from a Th2 to a Th1 comprising administering to the subject a composition comprising a CpG oligonucleotide (8-100 or 8-40 nucleotides long). The CpG oligonucleotide formulas are 5'X_1 X_2CGX_3X_4 3' and are non-palindromic. The claims, for example, define that X_1, X_2, X_3, and X_4 are any nucleotide. The claims define that the nucleic acid phosphate backbone has been modified. The routes of administration and delivery formulations have been defined as well.

It is noted that the specification teaches that the mechanism of immune response in the treatment of asthma is a redirecting of the subject's immune response from a Th2 to a Th1 immune response. The specification teaches that certain nucleic acids containing unmethylated CpG dinucleotides activate lymphocytes in a subject and redirect a subject's immune response from a Th2 to a Th1 (e.g. by inducing monocytic cells and other cells to produce Th1 cytokines, including IL-12, interferon gamma and GM-CSF) (see pp. 7-8). "In another embodiment, the invention provides a method of stimulating immune activation by administering the nucleic acid sequences of the invention to a subject, preferably a human. In a preferred embodiment, the immune activation effects predominantly a Thl pattern of immune activation." (p. 8, l. 20-23) "In addition, the nucleic acid sequences can be administered to stimulate a subject's response to a vaccine. Furthermore, by redirecting a subject's immune response from Th2 to Thl, the claimed nucleic acid sequences can be used to treat or prevent an asthmatic disorder. In addition, the claimed nucleic acid molecules can be administered to a

subject in conjunction with a particular allergen as a type of desensitization therapy to treat or prevent the occurrence of an allergic reaction associated with an asthmatic disorder." (p. 9, l. 7-12) The specification defines asthma as well as allergy and allergens (see p. 13). "Furthermore, the claimed nucleic acid sequences can be administered to treat or prevent the symptoms of an asthmatic disorder by redirecting a subject's immune response from Th2 to Th1. An exemplary sequence includes TCCATGACGTTCCTGACGTT (SEQ ID NO: 10)." (p. 17, l. 14-17). It is noted that SEQ ID NO: 10 is a non-palindromic sequence.

"Another use of the described immunostimulatory nucleic acid molecules is in desensitization therapy for allergies, which are generally caused by IgE antibody generation against harmless allergens. The cytokines that are induced by unmethylated CpG nucleic acids are predominantly of a class called "Th1" which is most marked by a cellular immune response and is associated with IL-12 and IFN-gamma. The other major type of immune response is termed a Th2 immune response, which is associated with more of an antibody immune response and with the production of IL-4, 11-5 and IL-10. In general, it appears that allergic diseases are mediated by Th2 type immune responses and autoimmune diseases by Thl immune response. Based on the ability of the immunostimulatory nucleic acid molecules to shift the immune response in a subject from a Th2 (which is associated with production of IgE antibodies and allergy) to a Thl response (which is protective against allergic reactions), an effective dose of an immunostimulatory nucleic acid (or a vector containing a nucleic acid) alone or in conjunction with an allergen can be administered to a subject to treat or prevent an allergy.

"Nucleic acids containing unmethylated CpG motifs may also have significant therapeutic utility in the treatment of asthma. Th2 cytokines, especially

lL-4 and IL-5 are elevated in the airways of asthmatic subjects. These cytokines promote important aspects of the asthmatic inflammatory response, including IgE isotype switching, eosinophil chemotaxis and activation and mast cell growth. Thl cytokines, especially IFN-gamma and IL-12, can suppress the formation of Th2 clones and production of Th2 cytokines.

"As described in detail in the following Example 12, oligonucleotides containing an unmethylated CpG motif (i.e., TCCATGACGTTCCTGACGTT; SEQ ID NO: 10) but not a control oligonucleotide (TCCATGAGCTTCCTGAGTCT; SEQ ID NO: 8) prevented the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma. Furthermore, the suppression of eosinophilic inflammation was associated with a suppression of a Th2 response and induction of a Thl response." (see p. 53, l. 12 to p. 54, l. 5) Cytokines that increase in relation to a Th1 immune response include interferon-gamma, TNF-beta and IL-12.

The specification discloses Example 12 (see pp. 63-64), prevention of the development of an inflammatory cellular infiltrate and eosinophilia in a murine model of asthma, which is a redirecting of the subject's immune response from a Th2 to a Th1 immune response. Mice were immunized with *Schistosoma mansoni* eggs (SEA) by i.p. injection on days 0 and 7. SEQ ID NO: 10 was administered to the immunized mice and soluble SEA was administered by intranasal instillation on days 14 and 21. After challenge the mice were sacrificed and cytokine levels and other assays conducted on the lavage fluids. The specification indicates that Figures 9-15 show that CpG/SEA induced inflammatory cells, eosinophils, to be present and generated macrophages; higher IL-12 was induced, IL-4 was reduced and IFN-gamma production increased. Applicants assert that the CpG redirected

the cytokine response of the lung to production of IL-12 and IFN-gamma, indicating a Th1 type immune response (p. 65).

The specification does not teach that any of the other myriad of possibilities of CpG having the claimed formulas can be used to treat an asthmatic subject (redirecting a Th2 to Th1 immune response), animal or human. The method of Example 12 teaches that CpG and the SEA were administered to the asthmatic subject at the same time. It is not clear from the example shown if the CpG administered alone to an asthmatic will redirect the cytokine responses and therefore Th1 type immune responses. The pending claims only recite that CpG is administered. It is not clear that the other claimed CpG sequences are sufficient to treat an asthmatic subject. The specification teaches *in vitro* methods and *in vivo* methods using SEQ ID NO: 10, a non-palindromic sequence, in a murine model for asthma, which is a redirecting of the subjects immune response from a Th2 to a Th1 immune response. It is not clear from the specification that the scope of the claimed invention is enabled.

The state of the art is unpredictable with regard to asthma treatments using CpG. CpG containing oligonucleotides are currently being investigated for exerting their immunotherapeutic effects in various organisms. Biological responses to the administration of CpG containing oligonucleotides vary, however, depending on the mode of administration and the organism (see McCluskie et al Molecular Med., 1999, 5/5:287-300 in its entirety, and especially on p. 296; see Krieg et al, Immunology Today, 2000, 21/10:521-526, especially p. 524). Wohlleben et al 2001 (TRENDS in Immunology, 2001, 22/11:618-626) have studied the effects of CpG on atopic disorders such as allergic asthma. CpG-ODNs have multiple stimulatory effects on lymphocytes, including DCs, macrophages, B

cells, natural killer (NK) cells and T cells (p. 619). The state of the art questions whether "CpG-ODNs can be used in humans to inhibit the development of asthma? In vitro experiments have shown clearly that human cells react to CpG-DNA in a similar manner to lymphocytes from rodents.... The results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders. However, treatments using CpG-ODNs rely both on innate and adaptive pro-inflammatory Th1 immune responses to inhibit Th2 responses. For this reason, harmful side-effects of the treatment need to be ruled out. Besides potential problem of inducing strong inflammatory responses at the site of exposure to allergen, the use of CpG-DNA could also have other serious side-effects. It has been reported that the application of CpG-ODNs can cause septic shock in mice. A further potential problem might be the development of autoimmune disease after application of CpG-DNA. Residual autoreactive T cells might become sufficiently activated to cause disease after encountering APCs that have been unspecifically activated by CpG-DNA." (p. 620, col. 2) Wohlleben et al teaches that all approaches that induce Th1 responses have the potential side-effects of Th1-cell-mediated inflammation, potentially causing serious tissue damage (p. 624, col. 1). Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179; Kline et al, J. Immunol., 1998, 160:2555-2559) teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model (p. L172, col. 2; see also p. L178, paragraph bridging cols. 1-2). Kline et al 2002 teaches that splenocytes from OVA-treated mice did not develop an antigen-specific Th1 phenotype. However, mice treated with CpG ODN and OVA had a

marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2).

Weiner (J. Leucocyte Biology, 2000, 68:456-463) states furthermore that the molecular mechanisms of CpG oligonucleotides' immunostimulatory effects are not yet understood (see p. 461). And while the biological effects of some chemical modifications have been studied for CpG containing oligonucleotides, such as 2'-O-methyl modifications, phosphorothioate internucleotide linkages and 5-methyl cytosine substitutions, the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable (see Agrawal et al Molecular Med. Today, 2000, 6:72-81, especially on pp. 78-80).

Further, Satoh et al (Fukushima Igaku Zasshi, 2002, 52/3:237-250, abstract only) teaches that CpG-ODN is responsible for worsening of allergic contact dermatitis. "S.c. applied CpG ODN one day before sensitization of naïve mice significantly enhanced the ACD to DNFB which showed severe edema with massive CD8+ T cell infiltration." (abstract) Satoh et al also teaches that "[T]hese results indicate that CpG ODN vaccinations may elicit and aggravate side effects such as harmful CD8+ T cell-mediated type IV hypersensitivity responses." (abstract) Dziadzio et al (Handbook of Experimental Pharmacology, 2004, 161(Pharmacology and Therapeutics of Asthma and COPD):273-285, abstract only) teaches that "[V]arious combinations of plasmid DNA, immunostimulatory oligonucleotide (ISS-ODN), and proteins have been studied in murine models to evaluate the effectiveness of DNA vaccination. The success in skewing the immune response towards a Th1 phenotype in mice still needs to be evaluated in humans. The use of DNA vaccination as a treatment for allergic disease remains a viable option for the future." (abstract) The state of the art, taken as a whole, is

still unpredictable with regard to the use of ISS-ODN in treating asthma in an asthmatic subject (human or otherwise) in need of such treatment.

The amount of direction or guidance presented in the specification and the presence or absence of working examples is a hindrance to practicing the claimed invention. Applicants have not provided guidance in the specification toward a method for redirecting a subject's immune response from a Th2 to aTh1 immune response comprising the administration of any immunostimulatory nucleic acid comprising the formula set forth in claim 42, for example. As previously stated the specification teaches an increase in immunomodulation in mice (and comprising conversion from a Th2 to a Thl immune response), and treatment of asthma in a mouse model comprising the administration of SEQ ID NO: 10 and antigen (SEA). One skilled in the art would not accept on its face the examples given in the specification as being correlative or representative of the successful treatment of asthma in any organism comprising the administration by any route of any immunostimulatory nucleic acid comprising the formula in the claims in view of the lack of guidance in the specification and known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in any and/or all organisms/subjects. The specification as filed fails to provide particular guidance which resolves the known unpredictability in the art associated with effects provided *in vivo* in any and/or all organisms upon administration via any route of CpG containing oligonucleotides, and further whereby treatment effects are provided in any and/or all organism for asthma, which is redirecting a subject's immune response from a Th2 to a TH1 immune response. The breadth of the claims is very broad and the quantity of experimentation required is undue. The quantity of experimentation required to

practice the invention as claimed would require the de novo determination of accessible target sites, modes of delivery and formulations of the CpG to target appropriate cells and/or tissues in any and/or all organisms/subjects, and further whereby treatment effects are provided for the claimed conditions. Since the specification fails to provide particular guidance for the treatment of asthma comprising administration by any route of any CpG containing oligonucleotide (claimed formulas), and since determination of these factors for a particular CpG containing oligonucleotide and for the particularly claimed conditions, route of administration and organism is highly unpredictable, it would require undue experimentation to practice the invention over the broad scope as presently claimed.

The examples provided of the induction of various interleukins in spleen, liver or thymus cells are not representative of the successful treatment of asthma, which is redirecting the subject's immune response from a Th2 to aTh1 immune response, using any CpG containing oligonucleotide. No correlation is taught in the instant disclosure between the ability of these CpG containing oligonucleotides to induce a Th1 response in vitro (e.g. amount of IL-6 induction) and their ability to treat asthma *in vivo*. An assumed common mechanism of action does not ensure enablement for treatment. Effective delivery to appropriate and concentration of a particular CpG containing oligonucleotide necessary for providing treatment for asthma (i.e. redirection from Th2 to Th1 immune response in a subject) for a particular CpG containing sequence are still highly unpredictable. The success of redirecting a subject's immune response from a Th2 to a Th1 immune response with SEQ ID NO: 10 is not necessarily representative or correlative of the ability to successfully redirecting a subject's immune response from a Th2 to a Th1

immune response with any of the generic sequences claimed and the myriad possibilities of CpG sequences encompassed by the claims. The *in vivo* treatment success for these generic sequences require undue experimentation beyond that provided in the instant disclosure.

7. No claims are allowed.

8. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

10. The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record in this application or in related application 09/337584.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to N. M. Minnifield whose telephone number is 571-272-0860. The examiner can normally be reached on M-F (8:00-5:30) Second Friday Off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette R.F. Smith can be reached on 571-272-0864. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

N. M. Mansfield
Primary Examiner
Art Unit 1645

NMM
March 7, 2005